## REMARKS

Claims 1, 2, 4, 6, 7, 19-23, 26, and 42-48 are pending in the present application. Claims 1, 7, 42, 43, 44, 47 and 48 have been amended. Claim 6 has been cancelled. New Claims 49 and 50 are presented. Claims 42-48 have been withdrawn *sua sponte* by the Examiner, where Applicants traverse this withdrawal for reasons presented below and request rejoinder and examination of Claims 42-48. Thus, Claims 1, 2, 4, 7, 19-23, 26, and 42-50 are presented for examination.

Support for claim amendments can be found throughout the specification and in particular, on page 1 at lines 11-13, page 12 at line 14-17, page 76, line 23 to page 80, line 17 (Examples 10 and 11), Figures 53 and 54, and in Claim 6 as originally filed. Cancellation of Claim 6 necessitated amendment of claims dependent therefrom. The claim amendments do not add new matter and entry of the amendments is requested.

### Traversal of Examiner's withdrawal of Claims 42-48

Applicants traverse the Examiner's *sua sponte* withdrawal of Claims 42-48, presented by Amendment filed March 26, 2007, on grounds that the Examiner erred in applying the Restriction Requirement mailed November 18, 2003, to Claims 42-48. Applicants request reconsideration of this withdrawal, and rejoinder and examination of Claims 42-48.

As noted in the Office Action, the claims of Group 8 of the Restriction Requirement mailed November 18, 2003, were elected for initial examination (*see*, Office Action (OA) page 2), where Group 8 was defined as "drawn to a multifunctional compound comprising an antigen binding region specific for a tumor-associated antigen." Applicants note that Group 8 was defined using the term "multifunctional compound" which provides for at least one additional functional domain besides an antigen binding region specific for a tumor-associated antigen. Furthermore, the recital in Claim 1 of at least one non-immunoglobulin portion having receptor or ligand function requires at least one additional functional domain besides an antigen binding region specific for a tumor-associated antigen. The claims cannot logically be limited to a "multifunctional compound" with a single functional domain. Thus, election of Group 8 does not preclude presentation of new claims that recite the elected antigen binding region specific for a tumor associated antigen and recite functional domains in addition to the elected functional domain.

Claims 42-43 recite specific embodiments of the antigen binding region specific for a tumor associated antigen, *per* Group 8. Claims 44-48 are to be searched pursuant to the election of Group 8, for their recital of embodiments of the non-immunoglobulin portion of

the claimed multifunctional compound comprising an antigen binding region specific for a tumor associated antigen. Therefore, Claims 42-48 should be rejoined and examined.

**Claim rejections**

Pending claims stand rejected under 35 USC §103 over combinations of cited prior art. To reject claims under 35 USC §103(a), the Examiner must make a *prima facie* case of obviousness, which requires meeting three basic criteria. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. MPEP §§ 2142, 2143. Here, no *prima facie* case of obviousness has been established and the rejections should be withdrawn.

Applicants note that the claim rejections in the Office Action include arguments based on construing "expressed in and secreted by a mammalian host cell" to make statements concerning product by process claims (OA, pages 5 to 6). Applicants point out that this claim element is not presently at issue and was not argued in the previous Amendment. An explanation of the relevance of this argument to the current claim rejections is requested.

***Rejection over Müller et al. in view of Shu et al.***

Claims 1, 2, 4, 6, 7, 19, 20, 21, 22, and 26 stand rejected under 35 USC §103 over Müller *et al.* in view of Shu *et al.*, on grounds that Müller *et al.* allegedly discloses a heterodimer with four functional domains (OA page 4, lines 14-15), and Shu *et al.* allegedly discloses "making and using a non-immunoglobulin portion having receptor or ligand function" (OA page 6, lines 18-19), and one of ordinary skill would allegedly "have been motivated to the claimed invention because Shu *et al.* teach interleukin-2 brought to the site of interest by an antibody binding to a tumor antigen is good for reducing considerable systematic toxicity." (OA page 7, lines 9-11)

No *prima facie* case of obviousness can be established because neither reference discloses or suggests a heterodimeric multifunctional compound including at least three functional domains having different receptor or ligand functions, wherein at least one of the functional domains includes a non-immunoglobulin portion having receptor or ligand function and at least one of the functional domains includes a scFv-fragment. Neither reference can cure the deficiency of the other reference with respect to the failure to teach or

suggest the claimed invention, and there is no teaching or motivation to modify the references to produce the claimed invention.

***Cited references do not teach the claimed invention***

To establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. MPEP §2143.03, citing *In re Royka*, 180 USPQ 580 (CCPA 1974) (emphasis added). Here, Claim 1 recites, *inter alia*, a multifunctional compound with at least three polypeptide functional domains having different receptor or ligand functions, wherein at least one of the functional domains comprises a non-immunoglobulin portion having receptor or ligand function and at least one of the functional domains comprises an scFv-fragment.

Müller *et al.* fails to disclose: (1) three functional domains having different receptor or ligand functions; and (2) a non-immunoglobulin portion having receptor or ligand function. Müller *et al.* is deficient because the "bispecific antibodies" disclosed by Müller *et al.* have only two different receptor or ligand functions. It is admitted in the Office Action that Müller *et al.* fails to disclose or suggest a non-immunoglobulin portion (OA page 6, lines 16-17). Applicants traverse the Examiner's position that Müller *et al.* allegedly discloses four functional domains, where this position is apparently based on construing each $V_H$ region and each $V_L$ region of each scFv as a separate functional domain (OA page 4, lines 10-15). Such a construction is clearly precluded by Claim 1, which recites that at least one of the functional domains comprises an scFv fragment. For each scFv fragment, both the $V_H$ region and the $V_L$ region are required to provide the specific antigen-binding receptor or ligand function of the scFv fragment, such that $V_H$ regions and $V_L$ regions cannot be construed as separate functional domains. Thus, Müller *et al.* is deficient because the disclosed "bispecific antibodies" have only two functional domains having different receptor or ligand functions, and no non-immunoglobulin portion.

Shu *et al.* fails to disclose: (1) the use of $C_H1$or $C_L$ (including $C_K$) constant domains (2) formation of heterodimers via constant domains; (3) a heterodimeric multifunctional compound; and (4) a heterodimeric multifunctional compound having at least three functional domains having different receptor or ligand functions. Shu *et al.* discloses a single-chain fusion protein SCIg-IL-2 that forms a homodimer of polypeptide chains linked by disulfide bonds in the hinge region, each chain having a $V_H$-$V_L$ functional domain derived from the CC49 antibody fused to C2, and IL-2 fused to C3, where the homodimer has only two different receptor or ligand functions.

The references do not teach or suggest all the claim limitations. Combining the disclosure of bispecific antibodies in Müller *et al.* with the disclosure of a homodimer in Shu *et al.*, each reference disclosing a compound having only two different receptor or ligand functions, does not teach or even suggest the claimed heterodimeric multifunctional compound with at least three functional domains having different receptor or ligand functions, wherein at least one functional domain comprises a non-immunoglobulin portion and at least one functional domain comprises an scFv-fragment.

***No motivation to modify the references***

Because the cited references, alone or in combination, fail to teach or suggest the claimed invention, Applicants conclude that the present obviousness rejection must require extensive modification of the cited references to make the claimed invention. As noted above, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. MPEP §2143.

"In determining the propriety of the Patent Office case for obviousness in the first instance, it is necessary to ascertain whether or not the reference teachings would appear to be sufficient for one of ordinary skill in the relevant art having the reference before him to make the proposed substitution, combination, or other modification." MPEP §2143.01, quoting *In re Linter*,173 USPQ 560, 562 (CCPA 1972). A statement that modifications of the prior art to meet the claimed invention would have been "within the ordinary skill of the art" is not sufficient to establish a *prima facie* case of obviousness without some objective reason to combine the teachings of the references. MPEP §2143.01, citing *Ex parte Levengood*, 28 USPQ2d 1300 (Bd. Pat. App. & Inter. 1993) (emphasis added). Furthermore, if the proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification. MPEP §2143.01 *In re Gordon*, 221 U.S.P.Q. 1125 (Fed. Cir. 1984).

Here, the Examiner has failed to establish: (1) how the primary reference Müller *et al.* would be modified in view of the secondary reference Shu *et al.* to produce the claimed invention; (2) whether "the reference teachings would appear to be sufficient for one of ordinary skill in the relevant art having the reference before him" to make the proposed modification (where the proposed modification was not disclosed by the Examiner); (3) whether it would even be possible to successfully modify the references to produce the claimed invention; and (4) where motivation to modify the references is found.

That is, the Examiner has failed to establish how the disclosure in Shu *et al.*, of a homodimer of identical polypeptide chains with only two different receptor or ligand functions, and teaching how to ensure homodimer formation by retaining certain amino acid sequences (page 235 left column), can be used to modify the bispecific antibodies of Müller *et al.*, which are heterodimers with only two different receptor or ligand functions and no non-immunoglobulin portion, to successfully produce the claimed heterodimeric multifunctional compound with at least three functional domains having different receptor or ligand functions, including at least one non-immunoglobulin portion and at least scFv-fragment. Further, the Examiner has failed to establish whether the reference teachings in Müller *et al.* and Shu *et al.* would be sufficient for one of skill in the art having the references "before him" to make the proposed modification (where the proposed modification was not disclosed by the Examiner).

Likewise, the Examiner has failed to address whether such a modification could render the bispecific antibodies of Müller *et al* unsatisfactory for their intended purpose, even if they could be modified to produce the claimed invention.

Furthermore, no objective reason for such a modification has been provided.

Therefore, no *prima facie* case of obviousness has been established.

***No expectation of success***

The prior art can be modified or combined to reject claims as *prima facie* obvious as long as there is a reasonable expectation of success. MPEP §2143.02, citing *In re Merck & Co., Inc.*, 231 USPQ 375 (Fed. Cir. 1986). Here, in the absence of a teaching of how or why the cited references could or should be modified to produce the claimed invention, the Examiner has failed to establish a reasonable expectation of success from such a modification.

***Conclusion***

Because no *prima facie* case of obviousness has been established, the claim rejections under 35 USC §103 over Müller *et al.*, and Shu *et al.* are improper and should be withdrawn

***Rejection over Müller et al. in view of Shu et al., further in view of Plückthun and Pack***

Claims 1, 2, 4, 6, 7, 19, 20, 21, 22, and 26 stand rejected under 35 U.S.C. §103(a) over Müller *et al.* in view of Shu *et al.*, and further in view of Plückthun and Pack. The confusing words "is withdrawn" are found after the statutory basis and the cited prior art for

the rejection (OA page 7, line 16), exactly as on page 7 at line 5 of the previous Office Action (August 2, 2006). Once again, Applicants will assume that the rejection stands.

***No prima facie case of obviousness can be made using the cited references***

The rejection is improper because Plückthun and Pack fails to cure the deficiency in Müller *et al.* in view of Shu *et al.*, to make a *prima facie* case of obviousness. It is admitted in the Office Action that Müller *et al.* does not disclose using the upper hinge region of human IgG3. Plückthun and Pack is cited for allegedly disclosing the use of the upper hinge region from human IgG3, such that it allegedly would have been obvious to substitute the linkers of Müller *et al.* with the upper hinge region of human IgG3 taught by Plückthun and Pack, with an expectation of success because each reference allegedly teaches how to make each element of the claimed invention.

As discussed above, the combination of Müller *et al.* and Shu *et al.* does not teach all the claim limitations, and there is no teaching, suggestion, or motivation to modify Müller *et al.* in view of Shu *et al.* to make the claimed invention. Substituting the linkers from the upper hinge region of human IgG3 disclosed in Plückthun and Pack fails to cure the deficiencies of the other references, and fails to produce the claimed invention. Therefore, no *prima facie* case of obviousness has been established because the references, alone and combination, not only fail to teach or suggest each element of the claimed invention, but also fail to provide a teaching and motivation to modify the references to produce the claimed invention, and fail to provide a reasonable expectation of success from such modification.

***Improper hindsight***

In the Office Action, it is argued that rejecting Claims 1, 2, 4, 6, 7, 19-22 and 26, which do not recite the upper hinge region of human IgG, was proper because Claims 1, 2, 4, 6, and 19-22 allegedly "also include the linker recited in claim 23" because "[o]therwise it would not a depend claim" [*sic*] (OA, page 8, lines 8-9). This is an improper "hindsight" argument based on the disclosure in the present specification, in particular Claim 23. A hindsight basis for an obviousness rejection is inappropriate and cannot sustain a *prima facie* case of obviousness. *In re Dembiczak*, 175 F.3d 50 USPQ2d, 1614

***Conclusion***

No *prima facie* case of obviousness has been established and therefore, the rejection under 35 USC §103 is improper and should be withdrawn.

## CONCLUSION

Claims 1, 2, 4, 6, 7, 19-23, 26, and 42-48 are pending in the present application. Claims 1, 7, 42, 43, 44, 47 and 48 have been amended. Claim 6 has been cancelled. New Claims 49 and 50 are presented. Claims 42-48 have been withdrawn *sua sponte* by the Examiner, and this withdrawal has been traversed, such that Claims 42-48 should be rejoined and examined. Thus, Claims 1, 2, 4, 7, 19-23, 26, and 42-50 are presented for examination and should be found in condition for allowance.

Please charge any fees associated with the submission of this paper to Deposit Account Number 033975. The Commissioner for Patents is also authorized to credit any overpayments to the above-referenced Deposit Account.

Respectfully submitted,

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